REMARKS

The Claims

Without acquiescing to the rejection and solely to advance prosecution, Applicant has canceled pending Claims 82-92 without prejudice or disclaimer. Claims 93-103 have been added and are directed to an antibody or fragment thereof which specifically binds to an epitope of a BB' loop or to an epitope of an EF loop of an osteoprotegerin binding protein of SEQ ID NO: 39.

The new independent Claims 93 and 103 correspond to canceled Claims 86 and 87 written in independent form. Support for Claims 95-98 is found at p. 17, lines 17-32 of the specification. Support for Claims 100 and 102 is found in Example 11, specifically starting at p. 47, line 9. The remaining new claims correspond to claims previously pending but now canceled.

Supplemental Information Disclosure Statement

Applicant submits separately in electronic form a Supplemental Information Disclosure Statement and respectfully requests that the references cited therein are considered and made of record in the present application.

Declaration of John K. Sullivan

Applicant attaches hereto as Exhibit A a Declaration of John K. Sullivan submitted during the prosecution of co-pending U.S. Serial No. 09/211,315 (now U.S. Patent No. 7,097,834) which describes properties of certain antibodies to OPGbp prepared as described in Example 11 of the present application, including antibodies raised against the BB' loop-cys and EF loop-cys peptides.

Rejections under 35 U.S.C. 102(e) or 35 U.S.C. 103(a) over Gorman et al. (U.S. Patent No. 6,242,586)

The rejection of Claims 82-92 under 35 U.S.C. 102(e) as anticipated by, or alternatively under 35 U.S.C. 103(a) as obvious over Gorman et al (hereafter "the '586 patent") has been maintained. Claims 82-92 have been cancelled thereby rendering at

least some of the arguments moot. To the extent that any of the arguments could be used to support the rejection of new Claims 93-103, Applicant disagrees and requests that the rejections be withdrawn.

With respect to claims directed to antibodies which bind to the BB' or EF loops of OPGbp, the Examiner makes the following assertions (p. 3, second paragraph of the Office Action of April 14, 2008):

> Given that OPGbp and 499E9 are the same protein, it appears that the blocking antibodies disclosed by Gorman et al. must bind the recited epitopes because they are blocking antibodies, and blocking antibodies bind the BB' and EF loops of OPGbp/499E9.
>
> ...a person of ordinary skill in the art would have a reasonable expectation of success in obtaining blocking antibodies that bind the BB' and EF loops since these loops are domains known to interact with physiological ligands as is discussed in the specification... .

In the first statement, the Examiner appears to argue that any disclosure of blocking antibodies to OPGbp inherently anticipates antibodies that bind to the either the BB' or the EF loops. However, subsequent work has shown that additional blocking antibodies directed to human OPGbp recognized a region of OPGbp distinct from either the BB' or EF loops. These antibodies are described in PCT Publication No. WO 01/62932 (see Example 10) which corresponds to U.S. Serial No. 09/791,153 cited by the Examiner as part of an obviousness-type double patenting rejection. Thus, blocking antibodies to human OPGbp do not necessarily recognize epitopes in the BB' and EF loops.

In the second statement, the Examiner asserts that an antibody binding the BB' or EF loop would be obvious since identification an epitope bound by an antibody is routine in the art and simply amounts to further characterization of a known antibody. The Examiner relies on the expectation of success of finding antibodies that bind BB' and EF loops since these loops were known to interact with physiological ligands *as is discussed in the specification* [Applicant's emphasis]. It should be emphasized that it was Applicant's disclosure that first taught the importance of the BB' and EF loops as potential contact points between OPGbp and its cognate receptor, and for the first time taught one skilled in the art to raise antibodies which bind to those regions in OPGbp. Yet, the Examiner is exploiting Applicant's teachings to reconstruct the invention in hindsight and to justify why one would be successful in identifying the claimed epitopes.

This rationale for obviousness is improper as the Examiner has not pointed to any teaching in the art on the importance of the BB' and EF loops in the binding of OPGbp to its receptor.

More importantly, the claims are directed to antibodies which recognize certain epitopes on OPGbp and inhibit osteoclast formation. Even if one were to identify blocking antibodies and the epitopes to which they bind, there was no teaching in the art to test those antibodies for their ability to inhibit osteoclast formation. One skilled in the art following the teachings of the '586 patent would have tested blocking antibodies for their ability to modulate inflammatory and/or immune responses (see col. 20, line 65 to col. 21, line 8 of the '586 patent) but not for inhibiting osteoclast formation.

In summary, the disclosure of blocking antibodies by the '586 patent does not anticipate the antibodies that bind to the BB' loop and inhibit osteoclast activity. In addition, one skilled in the art relying solely on the disclosure of the '586 patent would not have expected that an antibody binding to a BB' loop would have the function of inhibiting osteoclast activity. For these reasons, the rejection is improper and should be withdrawn.

In the Office Action of April 14, 2008 on pages 4 to 6, the Examiner maintains a number of previous arguments that Claims 82-92 are anticipated and/or obvious.

It is asserted that the '586 patent disclosure of blocking antibodies to murine 499E9 inherently anticipates antibodies which bind to human OPGbp and inhibit osteoclast formation, as antibodies that bind to murine 499E9 would be expected to cross-react with human OPGbp and antibodies which block OPGbp binding to its target would necessarily inhibit bone resorption. In view of the cancellation of Claims 82-92 and the addition of new claims 93-103, it is believed that these arguments are moot.

The Examiner maintains that the '586 patent describes and enables a human OPGbp polypeptide, citing *Rasmusson v. SmithKline Beecham* 75 USPQ2d 1297 (CAFC 2005). However, the quoted section only pertains to the standard of enablement under sections 112 and 102 and does not address Applicant's arguments in the response of July 25, 2007. In particular, the Examiner has not cited any relevant case law stating that the mere mention of the existence of a particular human polypeptide is sufficient to anticipate a later disclosed and claimed sequence of the same human polypeptide. In

view of the cancellation of Claims 82-92 and the addition of new claims 93-103, it is believed that these arguments are moot.

The Examiner attempts to refute an argument attributed to Applicant that "an ordinary artisan would not have been able to isolate human OPGbp/499E9 and that antibodies would not cross-react with the human polypeptide." (p. 5 of the Office Action). The Examiner has misunderstood Applicant's position. Applicant's response dated January 25, 2008 states that "[n]o evidence has been presented to suggest that screening with an anti-murine 499E9 antibody would *necessarily and without fail* identify human OPGbp as a cross-reactive protein" [Applicant's emphasis]. Applicant's argument was directed to alleged anticipation of the claimed subject matter by the '586 patent and whether any evidence existed for the assertion that an anti-murine 499E9 antibody would *always* cross-react with human OPGbp, and not whether one skilled in the art would be able to identify any anti-murine antibody that cross-reacted with the human protein.

A second argument attributed to Applicant is that antibodies which "specifically bind" human OPGbp only bind that molecule and do not cross-react. The Examiner has misunderstood Applicant's position. Applicant's response of January 25, 2008 states that the '586 patent "provides in Example 5 a method of preparing antibodies 'specific for 499E9'. Thus, the ['586] patent only teaches methods for making antibodies that are specific for murine OPGbp and not for human OPGbp". This statement makes no representation about the meaning of the term "specific binding" and it is noted that neither the '586 patent nor the present application give a definition of the term. In view of this, Applicant maintains that "specific binding" should have the same meaning in both the '586 patent and the present case. It is clear that a method of preparing antibodies that are "specific for 499E9" as disclosed in the '586 patent is not a teaching of a method for preparing antibodies that specifically bind human OPGbp.

In view of the cancellation of Claims 82-92 and the addition of new claims 93-103, it is believed that these arguments are moot.

The Examiner also argues that an epitope on a BB' (or EF) loop could be as small as six amino acids which allegedly would increase the certainty that an antibody directed to murine 499E9 would cross-react with human OPGbp. Given that an antibody

binding to an epitope on a BB' loop of OPGbp is neither anticipated nor rendered obvious by the '586 patent for the reasons stated above, the argument is moot.

Rejection under 35 U.S.C. 103(a) over Anderson et al. (U.S. Patent No. 6,740,522) in view PCT Publication No. WO 93/12227

The rejection of Claims 82-92 under 35 U.S.C. 103(a) over Anderson et al. (hereafter "the '522 patent") in view of PCT Publication No. WO 93/12227 has been maintained. The arguments are similar to those set forth in the corresponding 103 rejection over the '586 patent et al. Specifically, it is alleged that:

> ...Anderson does not disclose that his antibodies inhibit osteoclast formation or that his antibodies bind to a particular loop, such as the BB' and EF loops. However, Anderson does disclose that his antibodies block the binding of RANKL/OPGbp to RANK/OPG and inhibit RANK/OPG signaling. ...As such, any antibody that blocks binding and inhibits signaling must be binding the BB' and EF loops of RANKL/OPGbp.

Although it is tangential to this rejection, Applicant notes that RANK and OPG are not the same polypeptides but are in fact distinct molecules with different amino acid sequences.

As set forth above in the discussion of the rejections over the '586 patent, it was unexpected that an antibody binding to a BB' loop would have the function of inhibiting osteoclast activity and consequently the claimed subject matter is not obvious over the '522 patent. It is requested that the rejection be withdrawn.

Rejection under non-statutory obviousness type double patenting

The rejection of Claims 82-92 under obviousness-type double patenting has been maintained in view of Claims 45-69 of U.S. Serial No. 10/180,648, Claims 1-20, 22, 23, 25, 27, 29, 31-34, 36-38, 40, 42-50, 52, 59, 60, 62, 64-67 and 76-87 of U.S. Serial No. 10/408,901, and Claims 10-20, 27-29 and 40-53 of U.S. Serial No. 09/791,153.

The Examiner notes that a Notice of Abandonment had been mailed on September 7, 2007 in connection with U.S. Serial No. 09/791,153 and a petition to revive an unintentionally abandoned application had been filed on December 19, 2007.

Applicant notes that the petition to revive was granted on May 2, 2008 and the application is now currently pending.

Applicant also notes that U.S. Serial No. 10/180,648 has been issued as U.S. Patent No. 7,364,736.

Applicant maintains and reiterates his previous argument that the claims from the '648, '901 and '153 applications cannot anticipate or render obvious the present claims because they were initially presented in applications that were filed later than the present application. However, Applicant defers any further comment until a determination of allowable subject matter in the present application has been made.

CONCLUSION

Claims 93-103 are believed to be in condition for allowance and it is requested that the application be passed to issuance.

Respectfully submitted,

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